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Review

Immunometabolism in atherosclerosis: a new understanding of an old disease

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Atherosclerosis, a chronic inflammatory condition, remains a leading cause of death globally, necessitating innovative approaches to target pro-atherogenic pathways. Recent advancements in the field of immunometabolism have highlighted the crucial interplay between metabolic pathways and immune cell function in atherogenic milieus. Macrophages and T cells undergo dynamic metabolic reprogramming to meet the demands of activation and differentiation, influencing plaque progression. Furthermore, metabolic intermediates intricately regulate immune cell responses and atherosclerosis development. Understanding the metabolic control of immune responses in atherosclerosis, known as athero-immunometabolism, offers new avenues for preventive and therapeutic interventions. This review elucidates the emerging intricate interplay between metabolism and immunity in atherosclerosis, underscoring the significance of metabolic enzymes and metabolites as key regulators of disease pathogenesis and therapeutic targets.

Highlights

Immune cell metabolic reprogramming plays a pivotal role in the atherogenic environment, orchestrating a complex interplay between inflammatory processes and metabolic pathways within the arterial walls.

The signaling properties of certain metabolites play key roles in the immune response associated with atherosclerosis.

Metabolic pathways and metabolites are emerging as promising therapeutic targets in atherosclerosis, offering novel avenues for interventions to modulate immune responses and inflammatory processes implicated in disease progression.

Intersection of immunometabolism and atherosclerosis pathogenesis

Atherosclerosis is a life-threatening chronic inflammation resulting in a wide range of arterial diseases, such as myocardial infarction and ischemic stroke, and remains the leading cause of vascular death worldwide [1,2]. Despite successful interventions targeting both traditional and non-traditional risk factors for atherosclerosis, the high prevalence of the disease highlights the need for novel approaches toward targeting pro-atherogenic pathways [3].

Endothelial cell dysfunction and inflammatory activation that manifest in lesion-prone areas of the arteries upset the vascular tone and play a key role in initiation and promotion of atherosclerotic plaque formation [4]. The vascular endothelium has numerous functions including coordination of the inflammatory response [5,6]. Lining the inner layer of blood vessels, endothelial cells serve as the interface between blood and tissues, directly in contact with blood. Consequently, these cells are vulnerable to damage and inflammation induced by risk factors associated with atherosclerosis, such as obesity, hypertension, poor nutrition, hypercholesterolemia, smoking, or diabetes mellitus [7]. This susceptibility is particularly notable in regions of blood vessels where flow is disturbed, predisposing them to the development of atherosclerotic plaques [8].

Recently, a novel research field termed '**immunometabolism**' (see Glossary) has provided new insight into our comprehension of the immune system in both health and disease [9]. Immune cell metabolic reprogramming, which involves alterations in crucial intracellular metabolic pathways, such as glycolysis, the tricarboxylic acid (TCA) cycle, oxidative phosphorylation (OXPHOS), the pentose phosphate pathway (PPP), fatty acid synthesis (FAS) and β-oxidation, and amino acid metabolism, significantly regulates and shapes immune responses [10,11]. Moreover, metabolites derived from these pathways or from gut microbiota play key roles in the modulation of metabolic pathways in immune cells and rewire their proliferation, polarization, and migration to

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peripheral tissues [12–14], and hence may represent major players in the modulation of vascular inflammation in atherosclerosis.

A deeper understanding of metabolic reprogramming offers the potential for discovering immunoregulatory therapies aimed at preventing or treating metabolic inflammatory disease. In this review, the role of immune cells in atherosclerosis progression and the influence of metabolic pathways and metabolites on the metabolic adaptation of immune cells in atherogenic milieus are discussed. Indeed, we focus our discussion on macrophages and T lymphocytes, as these are the main immune cells whose metabolic contribution to atherosclerosis has been studied. Nevertheless, we will also touch upon other immune cells.

Steps in plaque formation

Consequent to the initial lesion to the endothelium, both innate and adaptive immune responses are triggered (Figure 1, Initial lesion). Circulating monocytes infiltrate subendothelial regions upon binding to adhesion molecules upregulated on the endothelial cells, leading to the accumulation of **intimal macrophages** [15] (Figure 1, Fatty streak). Furthermore, disturbed endothelial homeostasis facilitates the transportation and entrapment of low-density lipoprotein (LDL) into the subendothelial space [16], where it undergoes oxidation and is subsequently taken up by macrophages, leading to the development of **foam cells** (Figure 1, Initial lesion). Additionally, foam cells derived from vascular smooth muscle cells (VSMCs) exacerbate the vascular inflammatory response [3,17].

The accumulation of necrotic foam cells, cholesterol crystals, and cellular debris forms the lipid core of the atherosclerotic plaque (Figure 1, Fatty streak). The consequent upregulation of multiple chemokines and cytokines stimulates VSMCs to undergo proliferation and migration towards the intima, resulting in the synthesis of extracellular matrix components such as collagen and elastin (Figure 1, Atherosclerotic lesion). This process contributes to the formation of the fibrous cap and thickening of the arterial wall [18].

Subsequently, the plaques expand as fibrous tissues proliferate, thereby restricting blood flow (Figure 1, Fibrous plaque). In some cases, the fibrous cap thins because there is a decrease in the synthesis of extracellular matrix macromolecules, while in other cases, plaques may progress to accumulate a higher proportion of matrix and a lower proportion of lipid over time. Both types of plaques eventually culminate in thrombosis, either through plaque rupture or superficial erosion (Figure 1, Plaque rupture), consequently leading to **ST elevated myocardial infarction (STEMI)** or **non-ST elevated myocardial infarction (NSTEMI)** [19].

Plaque formation and vulnerability are not solely propelled by lipids but also by inflammation [19,20] (Figure 1, right). Changes in the composition of numerous immune cells, including macrophages, dendritic cells, T cells, B cells, mast cells, and neutrophils, as well as the modified release of cytokines, chemokines, and other bioactive molecules, disrupt the balance between inflammation and anti-inflammation at plaque formation sites [21]. For instance, vulnerable plaques have fewer regulatory T cells and more effector T cells compared with stable plaques [22,23].

Metabolic regulation of immune cell function in atherosclerosis

Immune cells rely on a diverse array of metabolic pathways to support their functions and responses to various stimuli. Glycolysis, the process of breaking down glucose into pyruvate, plays a central role in providing energy and biosynthetic precursors for rapid immune cell activation and proliferation [19,20]. OXPHOS, involving the utilization of substrates to produce ATP in the mitochondria, is crucial for sustaining long-term immune cell functions such as memory

Glossary

Anaplerosis: the formation of TCA cycle intermediates to replenish the extracted supplies.
Athero-immunometabolism: a study of the effect of metabolism on the functional role of immune cells in the development of atherosclerosis.
Efferocytosis: the process by which phagocytes internalize and degrade apoptotic cells.
Ferroptosis: an iron-dependent cell death that gives rise to lipid peroxidation and oxidative cell death.
Foam cells: a type of macrophage cell with a foamy appearance due to the accumulation of lipid droplets and cholesterol.
Glutaminolysis: the metabolic pathway of deamination and degradation of glutamine, producing ATP and anabolic carbons.
Immunometabolism: a field of research that focuses on the study of the links and crosstalk between cellular metabolism and immune cell function.
Intimal macrophages: macrophage cells that differentiate from monocytes after infiltrating the intima layer of blood vessels.
Lipogenesis: the metabolic pathway of fatty acid synthesis from non-lipid precursors.
Non-ST elevated myocardial infarction (NSTEMI): a heart attack without elevation of the ST segment on an electrocardiogram that happens due to a partial blockage of an artery and causes less damage to the heart muscle.
ST-elevated myocardial infarction (STEMI): ST is a wave segment on an electrocardiogram that shows no electrical activity in normal conditions and hence is flat. STEMI is a heart attack that shows a rise in the ST segment of the wave on the electrocardiogram and means that the heart muscle is in the process of dying due to blockage of a coronary artery.

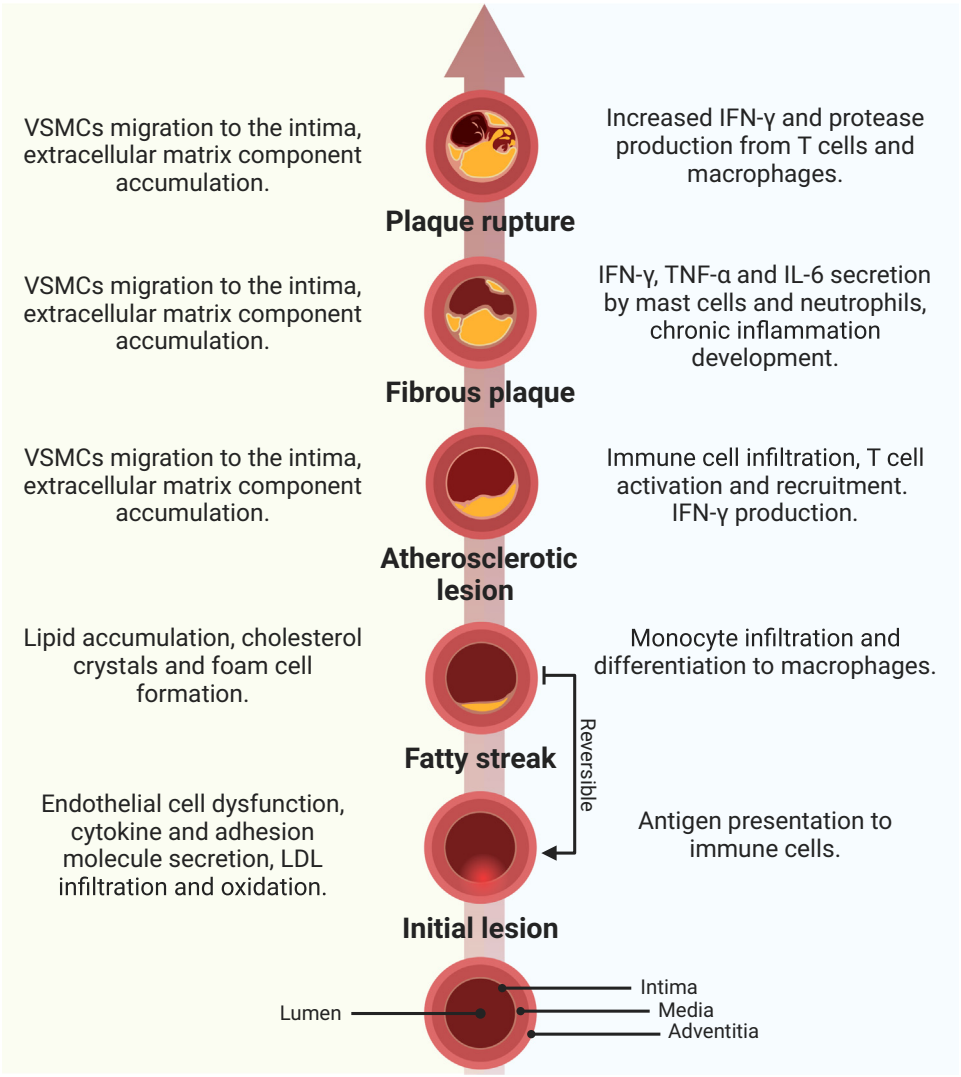

Figure 1. Atherosclerosis as a metabolic and chronic inflammatory disease. Damage to endothelial cells results in the release of adhesion molecules and the accumulation of intimal macrophages. The oxidation of LDL and the subsequent formation of foam cells intensify inflammation and the development of plaques. Plaque advancement occurs through lipid accumulation and production of extracellular matrix components, resulting in arterial wall thickening and the formation of fibrous caps. Concurrently, chronic inflammation ensues, as immune cells are recruited to the plaque site, secreting elevated levels of inflammatory mediators. Finally, plaque rupture leads to clinical complications. Abbreviations: IFN-γ, interferon-gamma; IL-6, interleukin 6; LDL, low-density lipoprotein; TNF-α, tumour necrosis factor alpha; VSMCs, vascular smooth muscle cells.

formation [19,20]. Additionally, regulated metabolic pathways of the three main nutrients, including carbohydrates, lipids, and amino acids, contribute to the metabolic flexibility of immune cells, influencing their differentiation, cytokine production, and effector responses [20]. The balance and coordination of these metabolic pathways are essential for maintaining immune cell homeostasis and mounting effective immune responses [11].

In recent years, research has unveiled the intricate interplay between metabolic pathways and immune cell function, shedding light on how metabolic reprogramming influences immune

responses in health and disease. This dynamic relationship between metabolism and immunity underscores the pivotal role of metabolic pathways in shaping the outcome of immune responses and opens new avenues for therapeutic interventions targeting metabolic checkpoints to modulate immune cell behavior. In the following section, we delve into the fundamental aspects of metabolism in macrophages and T lymphocytes, exploring how metabolic rewiring dictates their cell fate and function in the context of atherosclerosis.

Macrophages

The metabolic reprogramming of macrophages is a dynamic and intricate process that shapes their activation states and immune functions. Within atherosclerotic plaques, monocyte-derived macrophages play pivotal roles in multiple facets of disease pathogenesis. Through the uptake of modified lipoproteins, particularly oxidized LDL, macrophages transform into foam cells, leading to the accumulation of cholesterol esters and the initiation of plaque formation [24] (Figure 2). The classical activation of macrophages towards a proinflammatory phenotype promotes plaque progression by fostering oxidative stress, matrix degradation, and the recruitment of additional immune cells. Conversely, alternative activation of macrophages towards an anti-inflammatory, profibrotic phenotype may confer a protective role by promoting tissue repair, resolving

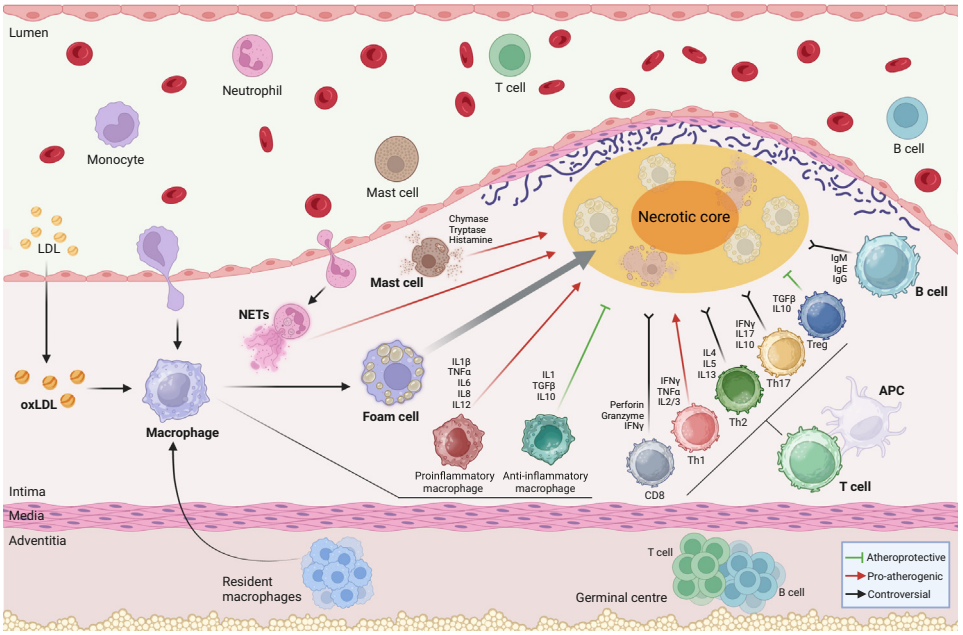

Figure 2. Immune cell functions in atherosclerotic disease. Immune cells play multifaceted roles throughout the different stages of atherosclerotic plaque development, contributing to both plaque initiation and progression, as well as its resolution or destabilization. Macrophages are key orchestrators within atherosclerotic lesions and are responsible for the uptake of oxidized lipoproteins (oxLDL), foam cell formation, and secretion of inflammatory mediators, driving plaque inflammation and progression. The balance between proinflammatory and anti-inflammatory macrophages critically influences plaque stability and vulnerability. T lymphocytes, including various subsets such as type 1 T helper (Th1), type 2 T helper (Th2), type 17 T helper (Th17), and regulatory T cells (Tregs), exert diverse effects on atherosclerosis. Effector T cells promote inflammation and plaque progression through cytokine production and interaction with macrophages. In some cases, they can have dual roles. Tregs suppress excessive inflammation and promote plaque stability by exerting immunoregulatory functions. Other immune cell populations, including B cells, mast cells, and neutrophils, also contribute to atherosclerotic plaque development and progression through various mechanisms, including antibody production and modulation of inflammatory responses. Abbreviations: APC, antigen-presenting cell; IFN-γ, interferon-gamma; IL, interleukin; LDL, low-density lipoprotein; NETs, neutrophil extracellular traps; TGF-β, transforming growth factor-beta; TNF-α, tumour necrosis factor alpha.

inflammation, and limiting lesion development [25] (Figure 2). Several studies have highlighted how changes in metabolism underlie this functional plasticity of macrophages [26].

The upregulation of glycolysis in proinflammatory macrophages supports their effector functions, such as phagocytosis, the production of reactive oxygen species (ROS), and the increase in interleukin (IL)-6 and IL-1β, as a consequence of dimerization and nuclear translocation of pyruvate kinase M2 (PKM2) [27]. The PPP is also upregulated, thus supporting the generation of metabolic intermediates, nucleotides, amino acids, and ribose, which contribute to a proinflammatory phenotype [28–30]. Furthermore, the TCA cycle is truncated, leading to accumulation of citrate and succinate [29], with the latter being linked with regulation of IL-1β [31]. In accordance with this metabolic reprogramming, it has been shown that macrophages within plaques exhibit heightened expression of glycolytic enzymes, leading to elevated levels of metabolites derived from both glycolysis and the PPP, including citrate, fumarate, and succinate [32]. Fatty acid metabolism also plays a significant role in macrophage function, linking FAS to atherosclerosis progression via inflammasome activation, epigenetic modifications, and immune responses [33,34]. FAS is involved in macrophage polarization, and it has been reported that ATP citrate lyase (ACLY), an enzyme catalyzing a key initial step in FAS, is upregulated in inflammatory macrophages in human atherosclerotic plaques [35]. In addition, deletion of fatty acid synthase (Fasn) reduces plaque formation in ApoE$^{-/-}$ mice [34]. By contrast, anti-inflammatory macrophages exhibit a preference for OXPHOS, an intact TCA cycle, and rely on mitochondrial respiration and fatty acid oxidation (FAO) to generate ATP and sustain long-term repair and regenerative processes, with potential anti-atherosclerotic effects [29,36] (Figure 3).

The metabolic rewiring of macrophages extends beyond energy production to the utilization of specific nutrients and metabolic intermediates to regulate immune responses. Arginine metabolism is a prime example of how metabolic pathways dictate macrophage polarization. Proinflammatory macrophages express inducible nitric oxide synthase (iNOS), which converts arginine to nitric oxide (NO) and citrulline, promoting a proinflammatory phenotype. Furthermore, anti-inflammatory macrophages upregulate arginase-1, which converts arginine to urea and ornithine, favoring tissue repair and immunoregulatory functions [37]. Questions have been raised over whether iNOS is indeed upregulated in circulating or infiltrating human M1 macrophages (differing from what is seen in murine macrophages), and the main source of iNOS seems to be tissue-resident macrophages [38]. In a recent study, it has been shown that in anti-inflammatory macrophages, the conversion of arginine, derived from apoptotic cells, into ornithine and then putrescine promotes **efferocytosis**, the process of clearing apoptotic cells, which aids in the resolution of atherosclerosis [39]. Moreover, glutamine metabolism influences macrophage activation, with glutamine serving as a critical substrate for the production of inflammatory cytokines and NO, and is associated with the development of atherosclerotic lesions [40]. **Glutaminolysis** is also implicated in the polarization of macrophages towards the anti-inflammatory phenotype, and it has been reported that enhanced α-ketoglutarate (αKG) is important for the activation of this type of macrophage through engagement of FAO and Jmjd3-dependent epigenetic reprogramming [41]. Furthermore, it has been reported that glutaminase (GLS) 1-mediated glutaminolysis plays a crucial role in promoting the clearance of apoptotic cells by macrophages, and impaired macrophage glutaminolysis increases atherosclerosis [42]. Finally, changes in intracellular iron metabolism within macrophages are intricately linked to macrophage polarization, the production of inflammatory mediators, and **ferroptosis**, all of which collectively influence the advancement of atherosclerosis [43].

T lymphocytes

T cells, a crucial component of the adaptive immune system, undergo metabolic reprogramming to support both protective and pathogenic processes, modulating the balance between immune activation and tolerance, inflammation, and tissue repair within atherosclerotic plaques. Unlike the

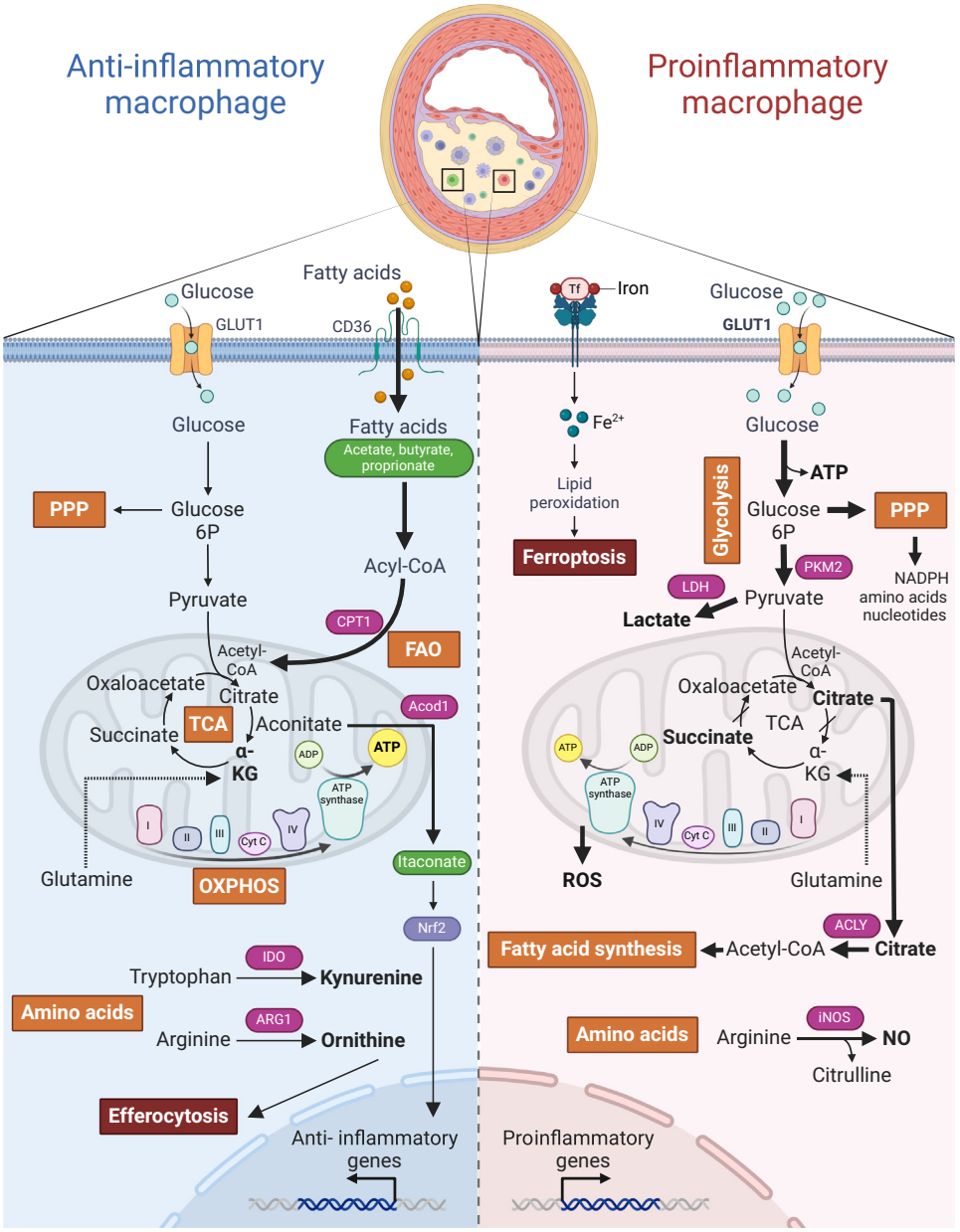

Figure 3. Metabolic pathways in macrophages in atherosclerosis. Macrophages play a central role in atherosclerotic plaque development and progression, exhibiting distinct metabolic phenotypes that influence their inflammatory status and functional properties. Proinflammatory macrophages, which are prevalent in advanced atherosclerotic lesions, undergo metabolic reprogramming characterized by enhanced glycolysis, activation of the pentose phosphate pathway (PPP), and increased fatty acid synthesis (FAS). These metabolic adaptations, together with increased ferroptosis, fuel the production of proinflammatory cytokines, reactive oxygen species (ROS), and damage-associated molecular patterns (DAMPs), exacerbating local inflammation and promoting plaque instability. By contrast, anti-inflammatory macrophages, typically found in early-stage lesions and during plaque regression, show a metabolic preference for oxidative phosphorylation (OXPHOS), the tricarboxylic acid cycle (TCA), and fatty acid oxidation (FAO). This metabolic profile, together with increased efferocytosis, support an anti-inflammatory phenotype, promoting tissue repair and resolution of inflammation within the plaque microenvironment. Abbreviations: ACLY, ATP citrate lyase; ACOD1, aconitate decarboxylase 1; α-KG, alpha-

(Figure legend continued at the bottom of the next page.)

classical view on atherosclerosis that sees macrophages as the dominant immune force, recent evidence from mass cytometry studies on human coronary arteries revealed that T cells outnumber macrophages in human carotid artery plaques [44]. This is in striking contrast to plaques in mice, in which the overall proportion of T cells is lower [45]. This suggests a much larger role of T lymphocytes in the pathogenesis of atherosclerosis than what decades of research in the field, largely driven by mouse-based research, had foreseen until recently.

The intracellular metabolism of T cells is tightly regulated to meet the energetic and biosynthetic demands associated with their activation, proliferation, differentiation, and effector functions, and regulates their contribution to disease progression [46].

Upon encountering antigens, naive T cells undergo a metabolic switch from a quiescent state sustained by OXPHOS [47] to an activated state marked by increased glycolysis, a hallmark of metabolic reprogramming in T cell activation [48,49] (Figure 4). This metabolic reprogramming contributes to the increased expression of glycolysis and PPP genes, including those encoding solute carrier family 2 member 1 (SLC2A1), solute carrier family 2 member 3 (SLC2A3), hexokinase 2 (HK2), hexokinase 3 (HK3), aldolase (ALDOA), enolase 1 (ENO1), 6-phosphogluconate dehydrogenase (6PGD), transketolase (TKT), and transaldolase (TALDO1), as well as the master regulators hypoxia inducible factor 1 subunit alpha (HIF1A) and MYC, in atherosclerotic plaques [50]. In addition, it has been shown that T cells in plaques overexpress pyruvate dehydrogenase kinases (PDKs), which are associated with upregulation of inflammatory pathways [51]. In the same study, the authors reported that targeting the PDK-pyruvate dehydrogenase (PDH) axis with the small-molecule PDK inhibitor dichloroacetate in ApoE$^{-/-}$ mice reshaped the immune system towards an anti-inflammatory phenotype, thus reducing vascular inflammation and atherogenesis, and promoting plaque stability. The shift towards aerobic glycolysis facilitates rapid production of ATP [52] and synthesis of metabolic intermediates necessary for T cell proliferation and effector functions [53,54]. Effector T cells, such as cytotoxic CD8 T cells and type 1 T helper (Th1) cells, favor glycolysis to support their rapid proliferation and effector responses. The increased glycolytic metabolism is usually accompanied by **anaplerosis**, in order to replenish TCA cycle intermediates. In patients with high-risk plaques, the levels of amino acids such as glutamine and serine are reduced compared with low-risk plaques, suggesting increased anaplerosis [50]. Recently, it has been reported that homoarginine reduces atherosclerosis in mice through a modulation of T cell actin cytoskeleton, leading to reduced proliferation and cell migration [55]. Furthermore, indoleamine 2,3-dioxygenase (IDO), which catalyzes the degradation of tryptophan in the kynurenine pathway, can counteract disease progression by promoting *de novo* FoxP3^{+} regulatory T cell (Treg) expansion [56]. Regulatory T cells and memory T cells exhibit a preference for OXPHOS to maintain immunosuppressive functions and long-lasting immune memory, respectively [57]. The balance between effectors and Tregs is also influenced by FAS, and it has been shown that inhibition of acetyl-CoA carboxylase 1 (ACC1) impairs the formation of human and mouse type 17 T helper (Th17) cells and promotes the development of anti-inflammatory Foxp3^{+} Treg cells [58]. As mentioned earlier, T cell activation also induces the PPP to produce building blocks for nucleotide and amino acid synthesis, alongside NADPH, which is crucial for maintaining reduced glutathione levels and sustaining lipid biosynthesis [59]. In parallel, T cells also rely on other metabolic pathways, such as glutamine metabolism, to fuel their activation and effector functions, highlighting the complex interplay between nutrient utilization and immune responses in T cells [60]. Cholesterol signaling during atherosclerosis has been shown to

ketoglutarate; ARG1, arginase 1; CPT1, carnitine palmitoyltransferase I; CytC, cytochrome C; GLUT1, glucose transporter 1; IDO, indoleamine 2,3 dioxygenase; iNOS, inducible nitric oxide synthase; LDH, lactate dehydrogenase; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PKM2, pyruvate kinase M2; Tf, transferrin.

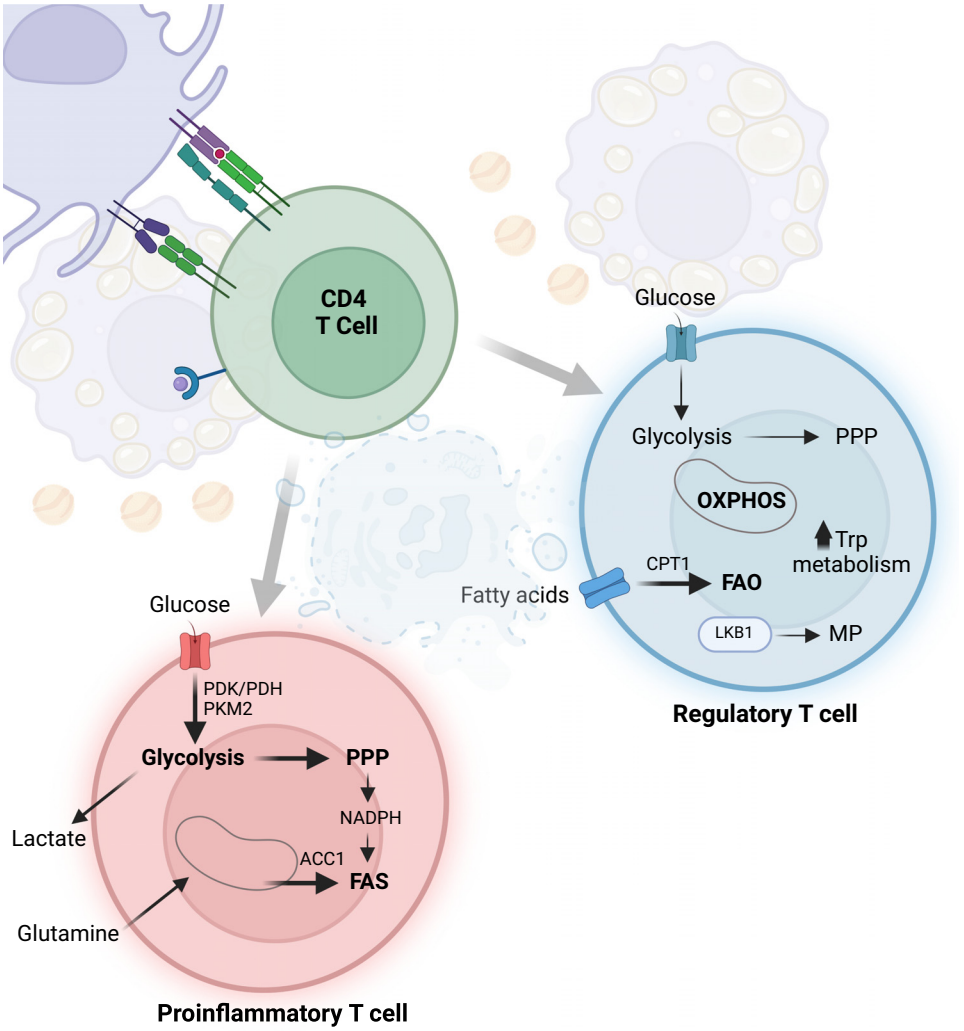

Figure 4. CD4 T cell metabolic profiles in the disease microenvironment. T cells undergo significant metabolic reprogramming within the context of atherosclerosis. Proinflammatory (effector) T cells, such as type 1 T helper (Th1) and type 17 helper (Th17) cells, exhibit a metabolic preference for glycolysis, pentose phosphate pathway (PPP) activation, and fatty acid synthesis (FAS), facilitating their proinflammatory functions and cytokine production. These metabolic pathways provide the necessary energy, cofactors, and biosynthetic precursors to sustain the heightened metabolic demands associated with T cell activation and effector responses. Conversely, regulatory T cells (Tregs), which possess anti-inflammatory and athero-protective properties, display a metabolic profile characterized by oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO), together with increases in tryptophan (Trp) metabolism and the mevalonate pathway (MP). This metabolic signature supports the suppressive functions of Tregs, contributing to the maintenance of immune tolerance and attenuation of atherosclerotic inflammation. Abbreviations: ACC1, acetyl-CoA-carboxylase 1; CPT1, carnitine palmitoyltransferase I; LKB1, liver kinase B1; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PKM2, pyruvate kinase M2.

alter T cell function, with increased levels of cholesterol promoting atherosclerosis progression through the conversion of Treg cells into effector T cells (Teff) cells [61,62].

Furthermore, metabolic intermediates and signaling pathways serve as critical regulators of T cell function and immune responses. For instance, mammalian target of rapamycin (mTOR) signaling integrates environmental cues, such as nutrient availability and cytokine signals, to orchestrate T

cell metabolism and differentiation [63]. Moreover, metabolites like lactate, acetate, and itaconate can modulate immune responses, inflammation, and immunometabolism in T cells, highlighting the multifaceted roles of metabolic intermediates in regulating T cell immunity [64,65]. More specific links between such metabolites and atherosclerosis are discussed in the next sections.

Other immune cells

The field of **athero-immunometabolism** is in its infancy, and if there is some initial evidence of the role of metabolic reprogramming of macrophages and T cells in atherosclerosis, almost nothing has been published so far for other immune cells.

Metabolite control of the immune response in atherosclerosis

Metabolites have been rediscovered over the past decade to be not mere intermediates of metabolism but as having signaling properties [66]. They can organize entire networks of crosstalk within and across tissues both in physiology and disease, such as succinate signaling in liver inflammation and muscle adaptation to exercise, or the lactate generated by glia in response to growth factors signaling a conducive environment for neuronal axon growth [67]. The role of some metabolites in atherosclerosis is only beginning to surface and is described later.

Lipid signaling

Lipids were initially recognized as structural components of cellular, organelle, and nuclear membranes. Recently, however, lipids and their metabolites have been increasingly acknowledged as key players in intricate signaling pathways that modulate immune cells in multiple ways, including their response to pathogens, phagocytosis, and inflammation, with implications in a range of metabolic diseases [68]. Thus, understanding how lipid metabolism can regulate immune cell response may be useful for potential therapies [69].

Current evidence suggests that a variety of macrophage phenotypes occur in atherosclerotic plaques, with local lipids and oxidized phospholipids altering their phenotype. Indeed, atherosclerosis-associated macrophage polarization dramatically affects the lipid-handling capacity of these cells, underpinned by major transcriptomic changes and altered levels of lipid-handling proteins [70].

Indeed, lipids and their metabolites are players in intricate signaling pathways that modulate macrophage responses to pathogens, phagocytosis, ferroptosis, and inflammation. While **lipogenesis** is crucial for lipid accumulation and phagocytosis in inflammatory macrophages, anti-inflammatory macrophages rely on lipid uptake and fatty acid β-oxidation to utilize fatty acids as their primary energy source (Figure 3). Cholesterol metabolism, regulated by factors such as sterol regulatory element binding proteins (SREBPs), peroxisome proliferator-activated receptors (PPARs), and liver X receptors (LXRs), is associated with the cholesterol efflux capacity and the formation of foam cells [68]. Foam cells, which are targets for atherosclerosis, are associated with an increase in inflammatory cytokines. Lipolysis and fatty acid uptake carriers, such as CD36, also contribute to the production of inflammatory cytokines in a feed-forward loop [71]. Hence, the traditional view that lipid accumulation passively promotes macrophage transition to foam cells is now being reassessed on the basis of the signaling properties of lipids and the interlinks between lipid signaling and immune pathways, such as for cytokines production.

Gut microbiota-derived metabolites

Microbial metabolites produced by the gut microbiome can modulate the expression of genes involved in cholesterol metabolism and inflammation, and hence control immune cell activation and polarization, with consequences for the cardiovascular system [72].

Short-chain fatty acids produced by the gut microbiome, such as acetate, butyrate, and propionate, can promote anti-inflammatory macrophage phenotypes and reduce atherosclerosis development (Figure 3). It was shown that butyrate inhibits monocyte attachment to injured endothelial cells by decreasing the synthesis of adhesion molecules, such as vascular cell adhesion molecule 1 (VCAM-1) and endothelial–leukocyte adhesion molecule 1 (E-selectin) [73]. Histone deacetylase (HDAC) was shown to be the enzyme mediating butyrate's repression of monocyte adhesion and VCAM-1 expression [74].

Haghikia *et al.* demonstrated that supplementation with propionate reduced total and LDL cholesterol levels in the blood. In ApoE$^{-/-}$ mice fed a high-fat diet, propionate reduced intestinal cholesterol absorption and aortic atherosclerotic lesion area. Propionate acted by increasing the number of Tregs and IL-10 levels in the intestine, which, in turn, suppressed the expression of Niemann–Pick C1-like 1 (Npc1l1), a major intestinal cholesterol transporter. Blockade of IL-10 receptor signaling attenuated the propionate-related reduction in total and LDL cholesterol and augmented atherosclerotic lesion severity [75]. In future studies, it would be interesting to see the effect of genetic inhibition of propionate synthesis by the gut microbiome on cardiovascular health and atherosclerosis. The authors went on to conduct a randomized, double-blinded, placebo-controlled human study (clinical trial No. NCT03590496). Oral supplementation with propionate significantly reduced LDL and non-high-density lipoprotein cholesterol levels [75].

Trimethylamine N-oxide (TMAO) produced by the gut microbiome can promote proinflammatory macrophage phenotypes and contribute to atherosclerosis development. By activating the farnesoid X receptor (FXR) and its small heterodimer partners, TMAO restricted the production of bile acid and facilitated the development of aortic lesions in atherosclerosis-prone ApoE$^{-/-}$ mice [76]. The capacity of TMAO to enhance the expression of CD36, the Class A1 scavenger receptor, and the cholesterol migration-associated gene ATP binding cassette transporter A1 (ABCA1) resulted in the accumulation of cholesterol in macrophages [77].

Overall, targeting microbial metabolites through dietary interventions, probiotics, or pharmacological approaches may be a potential therapeutic strategy for treating and preventing atherosclerosis.

Itaconate

Itaconate is an intermediate of the Krebs cycle that accumulates in lipopolysaccharide (LPS)-activated macrophages and initially highlighted for its antimicrobial properties [78]. In recent years, 4-OI, a derivative of itaconate, has been rediscovered as an anti-inflammatory metabolite that acts via the antioxidant transcription factor known as nuclear factor erythroid 2-related factor 2 (Nrf2) to limit inflammation [79] (Figure 3). Hence, it has been proposed as a therapeutic in a number of disease settings [80].

Perhaps unsurprisingly, then, a role for itaconate in atherosclerosis was also recently found. Three studies have recently reported a role for itaconate and its synthesizing enzyme, aconitate decarboxylase 1 (ACOD1, also known as IRG1), in protection against atherosclerosis [81,82]. Song *et al.* showed that itaconate and Acod1 are upregulated during atherogenesis in mice. Deletion of Acod1 in myeloid cells exacerbated inflammation and atherosclerosis *in vivo* and resulted in an elevated frequency of a specific subset of proinflammatory macrophages in the atherosclerotic aorta. Importantly, ACOD1 levels were inversely correlated with clinical occlusion in atherosclerotic human aorta specimens. Treating mice with the itaconate derivative 4-octyl itaconate attenuated the inflammation and atherosclerosis induced by high cholesterol. Mechanistically, they found that Nrf2 was required for itaconate to suppress macrophage activation induced by oxidized lipids *in vitro* and to decrease atherosclerotic lesion areas *in vivo* [82]. Harber *et al.* found

that atherogenesis-prone mice transplanted with Acod1$^{-/-}$ bone marrow displayed a more stable plaque phenotype with smaller necrotic cores and showed increased recruitment of monocytes to the vessel intima. Macrophages from Acod1$^{-/-}$ mice contained more lipids whilst also displaying reduced induction of apoptosis [81]. Finally, Cyr *et al.* [83] used cytometry by time of flight (CyTOF) and single-cell RNA-sequencing (scRNA-seq) of peripheral blood mononuclear cells treated with plasma from cardiovascular disease (CVD) patients to show that 4-OI attenuates pro-inflammatory phospho-signaling and mediates the anti-inflammatory rewiring of macrophage populations. Overall, these three studies highlight the relevance of pursuing IRG1-itaconate axis supplementation as a therapeutic approach for atherosclerosis in humans. Overall, the data point to the ACOD1-itaconate axis as potentially targetable for therapeutic gain.

Concluding remarks

Understanding the metabolic control of immune responses in atherosclerosis, 'athero-immunometabolism', is an emerging area, and metabolites and metabolic enzymes are the key to the regulation of such pathways. If we want to identify novel approaches to prevent or treat atherosclerosis, immunometabolism represents a goldmine. For instance, inhibitors of metabolic enzymes are being developed, such as those for PKM2, as they show promise for anti-inflammation approaches. Another avenue being explored is targeting microbial metabolites through dietary interventions, probiotics, or pharmacological methods for treating and preventing atherosclerosis. Similarly, itaconate is being developed for anti-inflammatory approaches in a plethora of diseases characterized by inflammation. Last, G protein-coupled receptor (GPCR) binding metabolites are likely to become a target of intense research in the near future, as the pharmacology for such receptors is well developed, holding promise for therapeutic gain (Box 1).

Related research work that will appear in the near future will resonate beyond the area of CVD and immunology, into the field of genetics. Those studying the associations between genetic characteristics and the risk of atherosclerosis are likely to identify mutations that occur in key genes that regulate metabolic pathways or control the entry and exit of metabolites into cells, adding new layers to previous known risk factors. Hence, the athero-immunometabolism field has the

Outstanding questions

What is the metabolic fuel of immune cell responses in human atherosclerotic plaques?

What metabolic enzymes, metabolite sensors, or metabolic supplements play key roles in atherosclerosis and can be harnessed to prevent, stabilize, or resolve the plaque?

How do systemic metabolic factors, such as obesity, diabetes, and dyslipidemia, influence immune cell metabolism and function in atherosclerosis, and can targeting systemic metabolism offer novel approaches for managing atherosclerosis?

Box 1. Metabolite-sensing G protein-coupled receptors (GPCRs)

GPCRs constitute the largest family of membrane proteins in mammals, and they participate in the regulation of major physiological functions in the organism. A growing number of GPCRs have now been identified as metabolite-sensing and are activated by intermediates of energy metabolism, including the free fatty acids (FFAs), lactate, succinate, and ketone bodies, among others, and play a key role in metabolic disorders [84,85].

GPCRs for long-, medium-, and short-chain fatty acids have been identified. They have been linked to inflammation and metabolic control, relating them to a range of metabolic conditions, from obesity to Type 2 diabetes. GPR91 was shown to be the unique receptor for succinate through experiments in GPR91 knockout mice, where administration of increasing doses of succinate raised the mean arterial blood pressure via increased secretion of renin in wild-type but not GPR91 knockout mice. However, GPR91 displayed a high EC_{50} for succinate (low millimolar) compared with physiological plasma levels of succinate (low micromolar), suggesting that the pathophysiological relevance of succinate may lie in situations where the blood supply to the kidney is restricted, such as renal atherosclerosis or ischemia [86].

Niacin has been known for a long time to be a potent agent controlling lipid levels in the plasma of patients at an increased risk of atherosclerosis. More recently, it was shown that niacin acts via GPR109A. Indeed, niacin was able to inhibit atherosclerosis in Ldlr$^{-/-}$ mice but not in Ldlr$^{-/-}$ Gpr109a$^{-/-}$ mice [87]. However, this area remains controversial, as another study concluded that in their animal model of atherosclerosis, the GPR109A receptor was not responsible for the beneficial lipid effects of niacin [88]. In addition to its anti-atherogenic effects on plasma lipids, niacin has anti-inflammatory effects, which have been ascribed to GPR109A-expressing immune cells [89].

Overall, studies are emerging to show that metabolite-sensing GPCRs may provide targets for the design of novel therapies for metabolic diseases, including atherosclerosis.

potential to fill the existing gap, whereby individuals that do not exhibit the known risk factors still suffer from infarcts or strokes, even at a young age (see Outstanding questions).

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Declaration of interests

The authors have no interests to declare.

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